

# NIEHS and EPA Children's Environmental Health and Disease Prevention Research Centers: *Strengthening the Network*

March 6–7, 2012 • NIH Campus, Bethesda, Md.



## SESSION 1: Plenary Session

### **Couple Based Approach for Assessing Environmental Pollutants and Human Reproduction and Development – Recent Findings from the LIFE Study**

*Germaine Buck Louis, National Institute of Child Health and Human Development (NICHD)*

The Longitudinal Investigation of Fertility and the Environment (LIFE) Study was designed to assess environmental pollutants and lifestyle in relation to a spectrum of reproductive and developmental outcomes. This talk will briefly address the LIFE Study's experience in overcoming key methodologic challenges underlying the design and conduct of population based research with preconception enrollment of couples planning pregnancies. In addition, emerging results regarding couples' exposures to persistent environmental chemicals and human fecundity as measured by time-to-pregnancy will be presented.

### **Environmental Epigenetics – Results and Opportunities for Children's Environmental Health and Disease Prevention Research**

*Andrea Baccarelli, Harvard School of Public Health*

Epigenetics investigates heritable changes in gene expression that occur without changes in DNA sequence. Several epigenetic mechanisms, including DNA methylation and histone modifications, can change genome function under exogenous influence. Results obtained from animal models indicate that in utero or early-life environmental exposures produce effects that can be inherited transgenerationally and are accompanied by epigenetic alterations. The search for human equivalents of the epigenetic mechanisms identified in animal models is in progress. I will present evidence from human environmental studies indicating that epigenetic alterations may mediate effects caused by exposure to environmental exposures. In these investigations, we have shown that environmental exposures are associated with altered methylation of human repetitive elements or genes, as well as with alterations of histone modifications. I will present original data demonstrating that altered epigenetic markings in blood and other tissues can be used to predict environmentally-induced disease, such as childhood asthma and cardiovascular disease. On the basis of current evidence, I will propose possible models for the interplay between the environment and the human epigenome, and outline opportunities and challenges in environmental epigenetics.



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## **Personalized Asthma Management: Addressing Environmental Impact**

*Stanley Szeffler, National Jewish Health*

Children are significantly affected by respiratory infections. In addition, respiratory viral infections are a major trigger of exacerbations in children with asthma. Asthma is a major public health problem that significantly affects children during the early stages of development. There is great interest in understanding the gene-environment interaction that leads to the development of asthma as well as the role of viral infections, air pollution and allergens in altering the course of the disease.

The Denver Childhood and Environmental Health Center Grant is directed at understanding the environmental determinants of airway disease in children. The clinical project is designed to understand the role of endotoxin as an environmental factor and genetic modifier that contributes to susceptibility and pathological asthmatic responses in children. Another project seeks to understand the role of ozone in the early postnatal phase in altering lung development and modifying the host immune response to early life viral infection and allergen exposure. A third project will evaluate toll-like receptor expression in the lung and how they are influenced by environmental and genetic factors. A Community Outreach Translational Core communicates information derived from these projects to community leaders in environmental health.

It is our hope that an integrated approach to basic and clinical science will lead to the identification of new epigenetic and biomarkers that can be used to predict asthma susceptibility and define new therapeutic targets for altering the course of respiratory disease in children including the development of asthma.

## **SESSION 2: New Emerging Tools and Technologies in Exposure Science**

### **Transcriptomics and Whole Genome Sequencing, Lessons Learned for the NCS**

*Elaine Faustman, University of Washington*

Formative research projects were conducted as part of the NCS that were designed to increase genomic capacity. We upgraded to next-generation (Illumina HiSeq 2000) instruments to create new sequencing capacity for these NCS projects. The specific goals of this research have been to examine the feasibility, acceptability, cost, scalability and informative value of genomic and transcriptomics information for the NCS. Samples available through the biorepositories of the Children's Health Centers have proven invaluable for making these comparisons. Specific application included the examination of within and across human variability for families using both a HiSeq method as well as a standardized DMET chip



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approach. Knowledge about individual genetic variability in terms of polymorphisms can improve our ability to predict and characterize variation in health responses after environmental exposure. Using such approaches, the team was able to sample over 60 families and determine polymorphisms in the cytochrome P450 pathways. Buccal cell DNA as well as blood buffy coat samples were used for these DNA and RNA analyses. Genotype call rates were high (>99%) and allele frequencies for two groups of genes, CYP450s and GSTs, were in concordance with results from other analyses of Hispanic populations. To better inform the gene-environment question and to better understand the potential health effects of environmental exposures we also used a transcriptomics approach to exposome-based analysis to provide a fingerprint for exposure. We are amplifying RNA from these sources to do this analysis. These examples for HiSeq and genomic analysis illustrate cost effective approaches for evaluating gene changes. Such feasibility and optimization studies illustrate new avenues for the Children's Health Centers to inform the NCS longitudinal study.

## Uncovering Early Life Metal Exposures Using Elemental Bio-Imaging of Teeth

*Manish Arora, Harvard University*

Measuring fetal exposure to multiple metal toxicants remains a major challenge in environmental epidemiology. Due to complex kinetics and variable partitioning across the placenta, metal concentrations in maternal blood, urine or other media in pregnancy may not accurately reflect fetal exposure for certain metals. A biomarker that can provide a direct measure of both the *intensity* and *timing* of exposure during intrauterine development would allow the efficient study of health outcomes of metal exposure during critical developmental events.

Deciduous teeth accumulate metals and their mineralization proceeds in an incremental pattern (akin to growth rings) spanning the prenatal and early postnatal periods. Therefore, teeth offer a potentially useful biomarker that can be applied to retrospectively reconstruct exposure.

This presentation will focus on the application of elemental bio-imaging – a technique that maps the distribution of metals at  $\mu\text{m}$  resolution – to the measurement of metals in teeth. The presentation will also include results from a series of animal and human studies that focus on two metals of public health significance – lead (Pb) and manganese (Mn). The significance of the proposed biomarker to case-control studies of rare diseases will also be discussed.



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## NTP Update: Systematic Review Incorporating Data Mining with Graphical Tools for Researchers

*Abee L. Boyles, NIEHS, NTP, Office of Health Assessment and Translation*

The NTP Office of Health Assessment and Translation (OHAT) is an environmental health resource that conducts evaluations to assess the evidence whether environmental exposures cause adverse health effects and provides opinions on whether these substances may be of concern to human health. Future OHAT literature reviews will be conducted under the principles of systematic review including explicit, transparent, and reproducible methodology. Individual study details and assessment of study quality will be captured in a consistent manner across studies. These data will accompany the written monograph of NTP conclusions and be made publically available. In conjunctions with these efforts, OHAT has developed a freely available graphical display tool, Meta Data Viewer, to facilitate data mining and visualization of large data sets, such as the ones created for evaluations. This tool was applied to data on maternal smoking and childhood obesity at the OHAT workshop “Role of Environmental Chemicals in the Development of Diabetes and Obesity” and will be utilized in the upcoming workshop “Clarifying Potential Health Effects of Excess Folic Acid Intake,” which will include evaluating childhood respiratory effects associated with folic acid supplement use during pregnancy.

### SESSION 3: Late Breaking Science

#### Pesticides and Child Health: Lessons from the Fields

*Brenda Eskenazi, University of California- Berkeley; Columbia University; Mt. Sinai*

Dr. Eskenazi has been working with the Latino farmworker population in the Salinas Valley. She will talk about children's exposures to pesticides and potential effects on health, development, and genetic susceptibility.

#### Rice and Rice Products as Potential Dietary Sources of Arsenic in Pregnant Women and Kids

*Margaret Karagas, Dartmouth College*

Emerging evidence indicates human exposure to arsenic by ingestion of foods such as rice; yet, little is known about this exposure during pregnancy or among children in the general population of the United States. As part of the formative Children's Environmental Health and Disease Prevention Research Center at Dartmouth we are investigating the impact of drinking water and food sources of contaminants such as arsenic on children's health. In New Hampshire, approximately 40% of the population relies on private, unregulated water systems, and over 10% of these systems have been found to contain arsenic



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above the current maximum contaminant level (MCL) of 10 micrograms/L. We have established a pregnancy cohort of women who use a private well at their home, and are measuring multiple biomarkers of arsenic exposure during pregnancy, in their newborns, and over their infants' first year of life. Preliminary work includes analysis of urinary arsenic in pregnant women in relation to both drinking water arsenic and diet (e.g., rice) (*Gilbert-Diamond et al., PNAS, 2011*). Pilot Project 2, led by Dr. Kathryn Cottingham, is performing a market basket survey of infant formulas, first foods, and later foods and is relating consumption to infant biomarkers (*Jackson et al., EHP, 2012*). Additionally, we have analyzed data from the National Health and Nutrition Examination Survey (NHANES) to investigate the relation between rice intake and urinary arsenic concentration among children (*Davis et al., under review*). Recognizing the need to identify sensitive biomarkers that may lead to earlier discovery, Center work embraces multidisciplinary studies of both biologic (e.g., immune, gene expression and epigenetic changes) and clinical outcomes (e.g., birth conditions and infections).

## Maternal Vitamin Intake and Autism

*Rebecca Schmidt, University of California- Davis*

Autism spectrum disorder (ASD) is an increasingly prevalent neurodevelopmental disorder affecting 1:110 children in the United States. Evidence supports large heritable contributions to the etiology of ASD, though environmental factors are likely to modify both the development and the course of ASD. A role for nutritional contributions, known to influence other neurodevelopmental outcomes, is suggested by a recently reported association linking short intervals between pregnancies and ASD.

We present findings from the large, population-based CHARGE (CHildhood Autism Risks from Genetics and the Environment) study suggesting that periconceptional use of prenatal vitamins may reduce the risk of having children with autism, especially for genetically susceptible mothers and children, and for those with certain other environmental exposures. A potential role for folate and epigenetic mechanisms will be discussed.

## Early Exposure to Bisphenol A and Lead: Effects on Metabolic Homeostasis and the Epigenome

*Dana Dolinoy, University of Michigan School of Public Health*

Environmental exposures during early development and other critical life stages may induce changes to the epigenome resulting in potentially deleterious phenotypic effects including metabolic disease, cancer, and neurological disorders. The field of epigenetics is experiencing a rapid advancement in technology,



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methodology, and data acquisition that now allows for the identification of the constellation of genomic loci with altered epigenetic status following dose-dependent exposures. Thus, epigenomic profiling facilitates the identification of biomarkers of exposure, enabling clinicians to identify at-risk individuals prior to disease onset. This presentation incorporates an overview of the University of Michigan P20 Center, “Perinatal Exposures, Epigenetics, Child Obesity & Sexual Maturation.” Utilizing a two-pronged approach with both an *in vivo* mouse model and an ongoing 15-year longitudinal epidemiological study (the Early Life Exposures in Mexico to Environmental Toxicants, ELEMENT, Cohort), the overall goal of our research is to elucidate the impact of perinatal lead and Bisphenol A exposure on childhood growth, DNA methylation, and the interplay between the two. This work is supported by EPA/NIH P20 RD834800/ES01817101.

## **SESSION 4: Communication Outreach and Translation Efforts to Protect Children from Environmental Threats**

### **A Partnership between CCCEH and WE ACT for Community Outreach and Engagement**

*David Evans, Columbia Center for Children's Environmental Health*

*Peggy Shepard, WE ACT for Environmental Justice*

*Brennan Rhodes, Columbia Center for Children's Environmental Health*

The Community Outreach and Translation Core (COTC) of the Columbia Center for Children's Environmental Health (CCCEH) and WE ACT for Environmental Justice (WE ACT) have worked together with our Community Advisory & Stakeholder Board (CASB) for 12 years to assess community environmental concerns and to translate and disseminate CCCEH research findings to the community. We will review COTC's accomplishments, provide an update on recent activities, and discuss opportunities for future collaboration.

### **Community Outreach and Engagement Addressing Environmental Health in a Multi-Faceted Agricultural Community**

*Daniel Madrigal, University of California- Berkeley (CHAMACOS)*

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) is a community/university partnership examining environmental exposures and children's health and development in the Salinas Valley, CA. To complement the research aims, the CHAMACOS community outreach and translation core (COTC) is engaged in extensive translational activities in this low-income, agricultural area, including: (1) timely dissemination of study findings to individuals, key stakeholders,



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and the general community, (2), providing a mechanism for community members to contribute to the research process and also help set priorities for future directions, (3) increasing awareness about children's environmental health, (4) targeted outreach to prevent toxicant exposures, (5) developing an environmental health leadership program for local adolescents, and, (6), when requested, educating policy makers about the implications of our research findings. Each of the community-engagement activities are targeted to populations with different education levels and personal and economic interests and thus require population-specific framing strategies to ensure effective, two-way, communication. In this presentation, the overall outreach program and the essential components of our framing strategy for each population will be described. We will also discuss future directions for the CHAMACOS COTC activities.

## **Community Assessment: Understanding the Built Environment within a Neighborhood Health Context**

*Pamela Maxson, Duke University*

Studies have shown that public health and individual quality of life are impacted not only by biological and socio-economic factors but by the built environment that people inhabit, although that relationship has never been systematically explained. The Community Assessment Project (CAP) was designed to elucidate the relationship between built environment variables and environmental, public health, and clinical health data for the city of Durham, North Carolina. Additionally, the project sought to create and refine a neighborhood assessment model that could be easily adapted by other researchers and community partners. CEHI first conducted the CAP during the summer of 2008, and in an effort to map the changes in Durham neighborhoods since that time, the assessment was conducted again during the summer of 2011.

A standardized visual assessment of 57 built environment variables was developed and implemented by trained assessors observing over 30,000 individual tax parcels throughout the city of Durham. Data observed were recorded in a database on handheld GPS units and then uploaded into a geodatabase stored on a secure server. This data was indexed, aggregated, and mapped to reflect Census Block-level neighborhood characteristics. A variety of thematic maps were developed in order to highlight neighborhoods with higher incidences of housing damage, property disorder, public nuisances, and territorial or security measures. Preliminary results suggest that some areas east and south of Central Durham have significant concentrations of these negative characteristics. The CAP assessment tool offers a practical and comprehensive inventory of the built environment in Durham. In an effort to identify ways to improve Durham's built environment, data will be disseminated via community outreach and meetings with local stakeholders.



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## SESSION 7: Communication & Translation Efforts at NIEHS and EPA

### **Making the Most of Your Media and Public Outreach Efforts**

*Ed Kang, NIEHS*

*Kelly Widener, EPA*

NIEHS and EPA are actively promoting the successes of the Centers for Children's Environmental Health and Disease Prevention. Collectively, we have a plethora of resources available to disseminate grantee research results to a diverse audience of mass and specialized media, advocates, government and academic institutions, and the general public. By using resources such as websites, media relationships, publication libraries, newsletters, science education tools, and social media, NIEHS and EPA garner a wide, international audience that can help increase the visibility and awareness of the Centers' research findings. In this session, NIEHS and EPA experts from their respective communications offices will explain these resources and the important factors grantees should consider when formulating an overall communications strategy.

### **Communicating with the Congress: For Better, For Worse, For ....**

*Mary Gant, NIEHS Congressional Liaison*

Congress, as the source of our laws and federal funds for research, exerts considerable influence over the direction of science and technology. It is essential for our society's well-being that congressional staff and members understand clearly the accomplishments, current activities, and needs of our national research enterprise. They will hear from advocates for a particular cause; they must hear from the research community who just come to the table armed with information from the peer-reviewed publications and a vision for the future.

### **The Program Analysis Branch: What is Our Role in Communicating Research Results?**

*Christie Drew, NIEHS, Program Analyses Branch*

Dr. Christie Drew will discuss recent activities in the NIEHS Program Analysis Branch to document and capture research results and impacts. Topics discussed will include the importance of citing grant numbers in publications, NIEHS papers of the month, the Evaluation Metrics Manual, a new tool that will help us track impacts, and emerging efforts to track trainee accomplishments.



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## SESSION 8: Breakout Sessions

### Sharing Environmental Health Data

*Kimberly McAllister, NIEHS*

*Symma Finn, NIEHS*

The purpose of this session is to gather information and recommendations from the environmental health science research community and others regarding best strategies that allow broad data sharing in the field of environmental health sciences in human population studies. NIEHS recognizes that environmental health science research is becoming increasingly complex and multidisciplinary. Therefore, the broad sharing of data generated from epidemiological studies is highly desirable to leverage the NIH investment in these studies and advance the field of environmental health sciences as a whole. These recommendations along with the recommendations from an accompanying RFI (request for information), entitled “Input on Strategies to Encourage Broad Data Sharing in Environmental Health Sciences Research”, will be considered by NIEHS for implementing a draft general data sharing policy.

### GWAS and Neurodevelopment

*Robert Wright, Harvard University*

*Cindy Lawler, NIEHS*

*Background:* A collaborative approach to studying gene–environment interaction could have immediate impact on our understanding of how environmental factors induce developmental disease and toxicity and will provide biological insight for potential treatment and prevention measures. Because DNA sequence is static, genetic studies typically are not conducted prospectively. This limits the ability to incorporate environmental data into an analysis, as such data is usually collected cross-sectionally in genetic studies. Prospective environmental data collection could account for the role of critical windows of susceptibility that likely correspond to the expression of specific genes and gene pathways. The use of large scale genomic platforms to discover genetic variants that modify environmental exposure in conjunction with a-priori planned replication studies would increase the speed of discovery, validate findings by reducing the number of false positive results. However, the measurement of environmental risk factors longitudinally is expensive and most environmental health studies have populations <1000 participants. Genome wide studies likely need sample sizes much larger than this. Pooling resources across multiple cohorts may be a cost effective method to conduct GXE interaction research that incorporates genomics, environmental exposures and critical developmental windows. A logical starting point for such studies would be pediatric birth cohorts.



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**Summary:** Using a genome-wide approach, combined with prospective longitudinal measures of environmental exposures at critical developmental windows is the optimal design for gene–environment interaction research. Perinatal/childhood diseases/development are ideal for this consortiums dedicated to studying GXE interaction. This approach would discover susceptibility variants, and then validate the findings in independent samples of children. Designs that combine the strengths and methodologies of environmental health and genetics will yield data that can account for both genetic variability and the role of critical developmental windows in the etiology of childhood disease and development. Finally, a consortium of birth cohorts would yield additional value such as the potential to study chemical mixtures as well as epigenetic changes, both of which would benefit from prospective exposure data.

## Challenges of QAQC in the Analyses of Epigenetic Markers in Human Studies

*Nina Holland, University of California- Berkeley*

*Kim Boekelheide, Brown University*

*Jaclyn Goodrich, University of Michigan School of Public Health*

*Richard Callan, EPA*

Epigenetic mechanisms, particularly DNA methylation, have attracted increasing interest in the etiology of disease, especially in regard to the hypothesized ‘fetal origins of disease’, and as a possible link between the genetic and environmental determinants of health. Methodologies for investigating DNA methylation have been rapidly emerging with increasing emphasis on genome-wide scale and throughput. The Illumina Infinium Human Methylation BeadChips, both 27 & 450k, are currently the leading platforms for simultaneous measurement of DNA methylation at a high volume of sites across the genome. To apply these new methodologies effectively in large epidemiological studies, adequate quality assurance and control (QAQC) measures need to be implemented to minimize technical variability. While traditional sources of experimental variability still apply to data produced by high-throughput platforms, including chip, batch, and between laboratory variability, several additional considerations are unique to DNA methylation analysis, including bisulfite-conversion efficiency, tissue specificity of methylation and the effects of age and sex.

We address the emerging QAQC challenges of high-throughput measurement of DNA methylation using samples drawn from a large longitudinal birth cohort. We measured DNA methylation in newborns and 9 year old boys and girls using both the Illumina Infinium HumanMethylation27K and 450K BeadChips. We provide a detailed characterization of data quality, including both technical and biological factors that contribute to DNA methylation variability. Development of a standardized assessment of highly-multiplexed DNA methylation data is necessary to ensure comparability and validity of data generated across laboratories and platforms.



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## Children's Environmental Research in Day Care and School Settings

*Asa Bradman, University of California- Berkeley*

*Patrick Ryan, Cincinnati Children's Hospital Medical Center*

*Nica Louie, EPA*

## Improving Environmental Quality in Childcare Centers

*Asa Bradman*

Nationally, there are ~13,000,000 children in childcare, with many children spending up to 10 hours per day, 5 days a week, in these facilities. Although many state and federal programs address environmental quality in K-12 schools, fewer resources have been directed to licensed preschools and childcare. In the last 15 years, a few studies have sampled environmental contaminants in childcare facilities or surveyed pest problems. These studies indicate that, like other indoor environments, allergens, VOCs, pesticides, lead, and other contaminants are present and significantly contribute to the total exposures experienced by young children. The surveys indicate that pest problems and pesticide use is common. And because of diapering and associated sanitation requirements, disinfectants and cleaners are heavily used, potentially affecting air quality. Local, state, and national non-profit and government agencies are beginning to develop research, education, and outreach programs to improve child care environments. For example, the 2000 California Healthy Schools Act, which requires notification of pesticide use and encourages integrated pest management, was extended to child care centers in 2007. This presentation will highlight research and outreach activities focusing on childcare by the Center for Environmental Research and Children's Health at UC Berkeley.

## Working with Schools to Conduct Environmental Health Research: An Example with Air Pollution and Asthma

*Patrick Ryan*

Children spend a significant portion of their time outside of the home. In particular, schools represent a setting where children may be exposed to both indoor and outdoor pollutants as well as an opportunity to work collaboratively with administrators, teachers, nurses and parents to conduct environmental health research. An example of this type of community-based research will be presented using the Cincinnati Anti-Idling Campaign study whose objectives are to 1) Determine if children are exposed to increased levels of air pollutants at schools compared to ambient levels in the communities where the children reside, 2) Develop and implement a community-driven anti-idling campaign aimed at reducing children's exposure to air pollutants, and 3) Evaluate the effectiveness of the research



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partnership and community-driven anti-idling campaign by assessing the reduction of exposure at schools and the impact on the health of children with asthma who attend these schools.



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